Appropriateness of Empirical Antibiotic Therapy in Bacterial Culture-Positive Inpatients: A Retrospective Cohort Study

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Research Article

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Abstract

Objectives

We aimed to evaluate the prevalence, relative factors, and outcomes of different empirical antibiotic therapy (EAT) prescriptions in infected inpatients.

Methods

We performed a retrospective cohort analysis of inpatients a tertiary hospital in China between October 1, 2019 and September 30, 2020. Bacterial culture-positive patients received EAT were enrolled in this study. We initially assessed the prevalence of different EAT prescriptions by univariate analysis, and then used an enter multivariable logistic regression model to calculate adjusted odds ratios for assessing relative factors and outcomes of them.

Results

1,257 infected patients received EAT on the day of sampling culture. 31.7% (398/1257) received appropriate but unnecessarily broad-spectrum empirical antibiotic therapy (AUEAT), and 37.3% (469/1257) received inappropriate empirical antibiotic therapy (IEAT). Age was a correlated factor of receiving AUEAT and IEAT. The odds of receiving AUEAT and IEAT increased with age (adjusted OR 1.023 [95% CI, 1.013 ~ 1.032]; p < 0.001; 1.009 [95% CI, 1.001 ~ 1.018]; p = 0.033). Patients who received AUEAT and IEAT had higher rates of ICU care and increased hospital costs. AUEAT has a higher proportion of poor prognosis (29.4%, 117/398, p < 0.001). Respiratory tract was the most common infection site (418/1257, 33.3%). The common pathogens were *Escherichia coli* (315/1257, 25.1%), *Klebsiella* species (208/1257, 16.5%), *Staphylococcus aureus* (204/1257, 16.2%), and *Pseudomonas* species (167/1257, 13.3%). 45.3% (570/1257) patients were infected with multidrug-resistant organism (MDRO), of which 53.5% (305/570) received IEAT. Among 305 MDRO infected patients with IEAT, 71.5% (218/305) were infected with Gram-negative bacteria. The majority of Gram-negative bacteria was *Enterobacteriaceae* (178/218, 81.7%), among which *E. coli* (116/178, 65.2%) and *Klebsiella* (38/178, 21.3%) strains accounted for high proportions.

Conclusions

Inappropriate or unnecessarily broad-spectrum use of antibiotics is widely prevalent in hospital. AUEAT and IEAT were bound to increase antimicrobial resistance, rates of ICU care, and health care costs. AUEAT was associated with increased risk of poor prognosis. Near half of inpatients infected with MDRO, and these patients were more likely to receive IEAT. Early identification of infectious pathogens and resistance can provide the basis for rational use of antibiotics and improve the current situation of antibiotic abuse and antimicrobial resistance.

Introduction

Appropriate antibiotic therapy is essential to ensuring positive outcomes of infected patients. Empirical antibiotic therapy (EAT) is unavoidable because most of the antibiotic treatment for the first 24 to 48 hours is empirical without evidence on the causative pathogen or its susceptibilities[1–3]. However, EAT could be discordant or excessive. In a previous systematic review, the prevalence of inappropriate empirical antibiotic therapy (IEAT) ranged from 14–79%[4]. And another review points out that half of intensive care unit (ICU) patients received broad-spectrum empirical antibiotic therapy with no definitively confirmed infection[5]. The current situation of IEAT and appropriate but unnecessarily broad-spectrum empirical antibiotic therapy (AUEAT) is serious around the world. IEAT and AUEAT would cause serious adverse event such as increase the generation of antimicrobial resistance, the prevalence of *Clostridioides difficile* infection, antibiotic-related toxicities, and health care costs[6–8]. In patients with bloodstream infection both IEAT and AUEAT are associated with increasing mortality[9]. Rational use of antibiotic and reducing the emergence of antimicrobial resistance have become global challenges[10].

In China, inappropriate antibiotic prescribing for outpatient was highly prevalent nationwide and over half of them occurred in secondary-level and tertiary-level hospitals[11]. Among the inpatients, compared with outpatients, antibiotic use was greater[12]. And inpatients were older and sicker at baseline, having higher costs across treatment periods, and the usage rate of β-lactamase inhibitor combinations increased with time[13,14]. Therefore, antibiotic use of inpatients needs more closely attention.

In our study, we investigated the prevalence, relative factors, and outcomes of EAT in infected inpatients, to provide information for clinical evaluation of patients and the strategy of antibiotic, thus increasing the proportion of rational use of antibiotics.

Methods

Study design and participants

We conducted a retrospective cohort study at a tertiary hospital in (Guangdong) China. The subjects we included were 68,740 patients aged at least 18 years admitted to hospital during October 1, 2019 to September 30, 2020. The inclusion criteria were patients with bacterial culture-positive and accepted EAT in hospitalization. The exclusion criteria included: 1) patients lacked of complete hospital records; 2) patients were not treated with antibiotics; 3) patients were not received antibiotics until 24 hours after sample culture; 4) patients without antimicrobial susceptibility test results. For patients with multiple admissions, we selected only the first admission and excluded subsequent admissions from the analysis and then included only the first culture specimen per patient. The study inclusion flowchart is shown in Fig. 1. Using our inclusion/exclusion criteria, 1,257 cases were finally included for analysis.

Data source

All data were extracted from electronic health record system. General and demographic patients characteristics were collected: age, sex, admitted departments, comorbidities (respiratory disease, hypertension, coronary heart disease, congestive heart failure, diabetes mellitus, renal failure, HBsAg positive, fatty liver, HIV, liver cirrhosis, autoimmune disease, transplant recipient, cancer, long-term use of hormones or immunosuppressants), smoking, alcohol drinking, previous bloodstream infection, fever, suspected site of infection (respiratory, urinary tract, skin or soft tissue, blood, abdomen, multisite, catheter-related bloodstream infection, other). To account for severity of disease, we performed Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score for each subject, clinically assessed whether they met the diagnostic criteria for sepsis/septic shock, and recorded the use of vasopressor, the use of colloid, mechanical ventilation, white blood cell count, neutrophil count (proportion of neutrophils), lymphocyte count, platelet count, hemoglobin, procalcitonin (PCT), C-reactive protein, erythrocyte sedimentation rate, prothrombin time, activated partial thromboplastin time, D-dimer, urea, serum creatinine, cystatin-C, alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin, troponin, brain natriuretic peptide, creatine kinase, lactate dehydrogenase, serum lactate, and Glasgow Coma Scale. ICU care, ICU length of stay (LOS), hospital LOS, hospital costs and patient outcomes were also included. Patient outcomes included cure/improvement, death, and discharge against medical advice. In a previous large national study, 1–2% inpatients discharge against medical advice, and increasing their risk of hospital readmission, morbidity, and mortality[15]. Therefore, we included discharge against medical advice and death in the analysis of poor prognosis of patients.

Microbiology data contained pathogens and antimicrobial susceptibility testing report. Bacteria were classified by Gram staining. We collected the empirical use of antibiotics during the hospitalization of each patient and evaluated the rationality of the antibiotic strategy based on the drug sensitivity test report, of which intermediate susceptibilities were treated as non-susceptible. The types of bacterial sensitivity could be classified into full sensitivity, single antibiotic resistance, two kinds of antibiotic resistance, multidrug-resistant organism (MDRO), extensively drug resistant (XDR), and pandrug resistant (PDR). Many bacteria have intrinsic antibiotic resistance (e.g., ceftriaxone and *Pseudomonas aeruginosa*) and were considered insensitive. When not reported for the antibiotic or antibiotics received, in-vitro susceptibility or resistance was imputed from interpretations that were reported within the same antibiotic category. For example, a Gram-negative organism susceptible to ceftriaxone may not have susceptibilities reported to all higher-generation cephalosporins (i.e., cefepime), but these agents can be safely used[9].

Definitions

EAT was defined as antibiotic treatment prior to the drug sensitivity tests report was obtained (at least 24 hours after sampling)[16]. Appropriate and necessarily empirical antibiotic therapy (ANEAT) was defined as patient was treat with empiric antibiotics, and the antibiotic regimen was active against the identified pathogen based on in susceptibility testing[17]. AUEAT was defined as the patient received empiric antibiotics and anti-methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotics, anti-vancomycin-resistant *enterococci* (VRE) antibiotics, anti-*Pseudomonas* β-lactam, or carbapenem, but none of these drug-resistant bacteria (MRSA, VRE, ceftriaxone-resistant Gram-negative organisms (CTX-RO), or extended-spectrum β-lactamase (ESBL) Gram-negative organism) was cultured at any infected site[9]. IEAT was defined as the patient was treated with empiric antibiotics, but at least one pathogen isolated from any clinical culture site was not sensitive to all antibiotics used[6,9]. MDRO is defined as non-susceptibility to at least one agent in three or more antimicrobial categories[18], including MRSA, VRE and certain Gram-negative bacilli[19]. XDR is defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories) [18]. PDR is defined as non-susceptibility to all agents in all antimicrobial categories (i.e., no agents tested as susceptible for that organism) [18]. Sepsis was defined according to Sepsis-3 criteria[20] as life-threatening organ dysfunction, which can be represented by an increase in the SOFA score of 2 points or more, caused by a dysregulated host response to infection. Septic shock was defined as a subset of sepsis, which used vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L (> 18 mg/dL) in the absence of hypovolemia.[20].

Data statistics

We calculated the overall and categorical prevalence of EAT. Based on our electronic health record system, we collected a high quality of data, with < 1% missing data across demographic variables. We did not conduct formal sample size calculations, and all available data were used to

maximize the power. Univariate analysis was performed on the collected baseline characteristics of patients (ANEAT vs AUEAT; ANEAT vs IEAT). Bivariate associations were assessed using the Pearson chi-square test or Fisher exact test for categorical variables and the students *t*-test or the Mann-Whitney *U* test for continuous variables. After the initial descriptive analysis of the cohort, we estimated the proportion of each covariate in different groups. To assess the relative factors of EAT with adjusted odds ratios (OR), all variables in the univariate analysis with $P < 0.1$ and *priori* variables were included in a enter multivariable logistic regression model. A *priori* we chose the following variables: sepsis or septic shock. These variables were included in each model irrespective of their statistical significance since they were considered having an important impact on outcome indicators in the clinical. In addition, we tried to include variables with $P < 0.1$, variables with $P < 0.2$ and re-screening variables without considering their statistical significance into the logistic regression model, and we finally obtained similar statistical results as before.

All tests of significance used a 2-sided $P < 0.05$. Analyses were conducted using IBM SPSS Statistic version 25.0.

Result

Patient Characteristics

We identified 1,257 patients with positive bacterial culture who received EAT (Fig. 1). 398 (32%) patients received AUEAT, and 469 (37%) patients received IEAT. The median age of 1,257 patients were 61 years old (interquartile range [IQR], 48–71) (Table 1). 723 (57.5%) patients were male. 191 (15.2%) patients with fever at admission, of whom 88 (46.1%) received AUEAT. SOFA scores increased ≥ 2 points in 187 (14.9%) patients. 177 (14.1%) patients with sepsis or septic shock, of whom 52.0% (92/177) received AUEAT. 154 (12.3%) patients were treated with vasopressor drugs after admission, of which 47.4% (73/154) patients received AUEAT. Colloid therapy was used in 298 (23.7%) patients and mechanical ventilation was used in 205 (16.3%) patients after admission, more than two-thirds of whom received AUEAT or IEAT. The characteristics of laboratory indicators data of 1257 patients are presented in Supplementary Table S1.

Table 1
Characteristics of 1257 patients with EAT

	Total(n = 1257)	ANEAT(n = 390)	AUEAT(n = 398)	*P* value	IEAT(n = 469)	*P* value
Demographic Characteristics						
Age, median (IQR), y	61(48–71)	57(46–68)	64(53–73)	<.001	60(48–71)	.048
Sex				.647		.736
Female	534(42.5%)	166(42.6%)	163(41.0%)		205(43.7%)	
Male	723(57.5%)	224(57.4%)	235(59.0%)		264(56.3%)	
Comorbidities [a]						
Respiratory disease	269(21.4%)	62(15.9%)	116(29.1%)	<.001	91(19.4%)	.181
Hypertension	435(34.6%)	125(32.1%)	145(36.4%)	.195	165(35.2%)	.334
Coronary heart disease	114(9.1%)	38(9.7%)	43(10.8%)	.624	33(7.0%)	.152
Congestive heart failure	89(7.1%)	25(6.4%)	35(8.8%)	.207	29(6.2%)	.892
Diabetes mellitus	279(22.2%)	82(21.0%)	100(25.1%)	.172	97(20.7%)	.902
Renal failure	125(9.9%)	33(8.5%)	48(12.1%)	.960	44(9.4%)	.638
HBsAg positive	98(7.8%)	32(8.2%)	31(7.8%)	.829	35(7.5%)	.686
Fatty liver	72(5.7%)	20(5.1%)	22(5.5%)	.803	30(6.4%)	.429
HIV	15(1.2%)	5(1.3%)	4(1.0%)	.714	6(1.3%)	.997
Liver cirrhosis	35(2.8%)	13(3.3%)	17(4.3%)	.491	5(1.1%)	.021
Autoimmune disease	61(4.9%)	24(6.2%)	19(4.8%)	.394	18(3.8%)	.117
Transplant recipient	18(1.4%)	5(1.3%)	6(1.5%)	.787	7(1.5%)	.794
Cancer	365(29.0%)	108(27.7%)	116(29.1%)	.651	141(30.1%)	.446
Using hormones or immunosuppressants	82(6.5%)	24(6.2%)	29(7.3%)	.526	29(6.2%)	.986
Previous bloodstream infection [b]	47(3.7%)	9(2.3%)	19(4.8%)	.062	19(4.1%)	.152
Smoking	207(16.5%)	57(14.6%)	72(18.1%)	.187	78(16.6%)	.419
Alcohol drinking	99(7.9%)	25(6.4%)	38(9.5%)	.104	36(7.7%)	.472
Infection Characteristics						
Fever	191(15.2%)	50(12.8%)	88(22.1%)	.001	53(11.3%)	.495
Increased SOFA score on the day of admission						
0	938(74.6%)	302(77.4%)	269(67.9%)	<.001	367(78.6%)	.771
1	128(10.2%)	48(12.3%)	32(8.1%)		48(10.3%)	

EAT: empirical antibiotic therapy; ANEAT: appropriate and necessarily empirical antibiotic therapy; AUEAT: appropriate but unnecessarily broad-spectrum empirical antibiotic therapy; IEAT: inappropriate empirical antibiotic therapy. These are the same in the following tables. IQR: interquartile range. SOFA: Sequential Organ Failure Assessment.

[a] Comorbidities were definitely diagnosed by clinician. Respiratory diseases mainly refer to chronic obstructive pulmonary disease, asthma, bronchitis, and other chronic respiratory diseases. Fatty liver was not clearly classified in this study. In addition to organ transplants, transplant recipients also included bone marrow stem cell transplants. Patients who using hormones or immunosuppressants specifically referred to the long-term users. [b] Clinicians may choose antibiotics with reference to the bacteria of their previous infections. [c] Vasopressor mainly refer to dopamine, norepinephrine or isoproterenephrine. [d] Refers to colloid dilatation treatment such as albumin, plasma or cryoprecipitation received during hospitalization. [e] Mechanical ventilation included high flow oxygen therapy, non-invasive auxiliary ventilation and invasive auxiliary ventilation therapy, and moderate or low flow oxygen therapy was excluded.

	Total(n = 1257)	ANEAT(n = 390)	AUEAT(n = 398)	*P* value	IEAT(n = 469)	*P* value
2	33(2.6%)	5(1.3%)	20(5.1%)		8(1.7%)	
≥ 3	154(12.3%)	35(9.0%)	75(18.9%)		44(9.4%)	
Severity of infection						
Sepsis	109(8.7%)	25(6.4%)	57(14.4%)	<.001	27(5.8%)	.342
Septic shock	68(5.4%)	11(2.8%)	35(8.8%)		22(4.7%)	
Common infections	1076(85.6%)	354(90.8%)	304(76.8%)		418(89.5%)	
Vasopressor [c]	154(12.3%)	32(8.2%)	73(18.3%)	<.001	49(10.4%)	.263
Colloid [d]	298(23.7%)	68(17.4%)	111(27.9%)	<.001	119(25.4%)	.005
Mechanical ventilation [e]	205(16.3%)	36(9.2%)	89(22.4%)	<.001	80(17.1%)	.001

EAT: empirical antibiotic therapy; ANEAT: appropriate and necessarily empirical antibiotic therapy; AUEAT: appropriate but unnecessarily broad-spectrum empirical antibiotic therapy; IEAT: inappropriate empirical antibiotic therapy. These are the same in the following tables. IQR: interquartile range. SOFA: Sequential Organ Failure Assessment.

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Infection Sites of Different EAT Prescriptions

Respiratory tract was the most common infection site (418/1257, 33.3%), followed by urinary tract infection (337/1257, 26.8%), skin and soft tissue infection (163/1257, 13.0%), and bloodstream infection (130/1257, 10.3%) (Table 2). Patients with respiratory tract infection and abdominal infection had higher proportion of receiving AUEAT and IEAT (respiratory: 177/418, 42.3% and 150/418, 35.9%; abdominal: 41/99, 41.4% and 38/99, 38.4%), while patients with skin and soft tissue infection were more likely to receiving ANEAT (70/163, 42.9%). Nealy half of patients with bloodstream infection (60/130, 46.2%) receive AUEAT. 45.7% (154/337) of patients with urinary tract infection received IEAT.

Table 2
Infection Site and Pathogen with EAT

	Total(n = 1257)	ANEAT(n = 390)	AUEAT(n = 398)	IEAT(n = 469)
Suspicious site of infection				
Respiratory	418(100.0%)	91(21.8%)	177(42.3%)	150(35.9%)
Urinary tract	337(100.0%)	133(39.5%)	50(14.8%)	154(45.7%)
Skin or soft tissue	163(100.0%)	70(42.9%)	38(23.3%)	55(33.7%)
Blood	130(100.0%)	35(26.9%)	60(46.2%)	35(26.9%)
Abdominal	99(100.0%)	20(20.2%)	41(41.4%)	38(38.4%)
Multisite	82(100.0%)	29(35.4%)	27(32.3%)	26(31.7%)
Other	16(100.0%)	6(37.5%)	2(12.5%)	8(50.0%)
Catheter-related bloodstream infection	12(100.0%)	6(50.0%)	3(25.0%)	3(25.0%)
Pathogen				
Escherichia coli	315(100.0%)	115(36.5%)	69(21.9%)	131(41.6%)
Klebsiella species	208(100.0%)	65(31.3%)	99(47.6%)	44(21.2%)
Staphylococcus aureus	204(100.0%)	66(32.4%)	55(27.0%)	83(40.7%)
Pseudomonas species	167(100.0%)	35(21.0%)	74(44.3%)	58(34.7%)
Enterococcus species	91(100.0%)	32(35.2%)	18(19.8%)	41(45.1%)
Acinetobacter species	55(100.0%)	5(9.1%)	10(18.2%)	40(72.7%)
Streptococcus species	51(100.0%)	20(39.2%)	30(58.8%)	1(2.0%)
other bacterial	166(100.0%)	52(31.3%)	43(25.9%)	71(42.8%)

Pathogens Characteristics of Different EAT Prescriptions

The common pathogens were *Escherichia coli* (315/1257, 25.1%), *Klebsiella* species (208/1257, 16.5%), *S. aureus* (204/1257, 16.2%), and *Pseudomonas* species (167/1257, 13.3%) in total (Table 2). More than two thirds of the *E. coli* strains were MDRO (Supplementary Fig. S1). Among patients received AUEAT, the largest quantity of positive bacteria in vitro culture was *Klebsiella* (99/208, 47.6%), followed by *Pseudomonas* (74/167, 44.3%), *E. coli* (69/315, 21.9%), and *S. aureus* (55/204, 27.0%). Strains of *E. coli* were the most numerous in patients who received IEAT (131/315, 41.6%), followed by *S. aureus* (83/204, 40.7%) and *Pseudomonas* (58/167, 34.7%).

Of the 1,257 patients, 570 (45.3%) were infected with MDRO, XDR, or PDR (Table 3). 53.5% (305/570) patients received IEAT and only 25.1% (143/570) received ANEAT. Among 305 patients infected with MDRO and received IEAT, 218 (71.5%) were infected with Gram-negative bacteria and 87 (28.5%) were infected with Gram-positive bacteria (Supplementary Table S2). The majority of Gram-negative bacteria were *Enterobacteriaceae* (178/218, 81.7%). The Gram-positive bacteria were mainly *Staphylococcaceae* (61/87, 70.1%). The most common site of infection in these patients was urinary tract infection (123/305, 40.3%), followed by respiratory tract infection (74/305, 24.3%). Among 178 patients with *Enterobacteriaceae* infection, 103 (57.9%) patients were treated with antibiotics that predominate cover Gram-negative bacteria but failed to cover MDRO, and 44 (24.7%) patients were treated with antibiotics that mainly cover with Gram-positive bacteria (Supplementary Table S3). 14.7% (32/217) patients infected with multidrug-resistant Gram-negative bacteria were treated with antibiotics that covered multidrug resistant Gram-negative bacteria, but didn't match the results of drug susceptibility tests in vitro.

Table 3
EAT and Antimicrobial Susceptibility Testing Report

	Total(n = 1257)	ANEAT(n = 390)	AUEAT(n = 398)	IEAT(n = 469)	P value
full sensitivity	295(23.5%)	98(33.2%)	138(46.8%)	59(20.0%)	< .001
one or two kinds of antibiotic resistance	392(31.2%)	149(38.0%)	138(35.2%)	105(26.8%)	
MDRO/XDR/PDR	570(45.3%)	143(25.1%)	122(21.4%)	305(53.5%)	
MDRO: multidrug-resistant organism; XDR: extensively drug resistant; PDR: pandrug resistant.					

In patients with respiratory tract infection, the most common culture-positive bacteria were *Klebsiella* species (109/418, 26.1%), followed by *Pseudomonas* species (97/418, 23.2%), *S. aureus* (54/418, 13.0%), *Acinetobacter* species (35/418, 8.4%), and *E. coli* (30/418, 7.2%) (Supplementary Fig. S2). The proportion of receiving AUEAT (54/109, 49.5%) was the highest in *Klebsiella* species culture-positive patients; similar results were found in patients who with *Pseudomonas* culture-positive. The most common culture-positive bacterium in urinary tract infections is *E. coli* (157/337, 46.6%) with more than two-thirds of them are MDRO and nearly half of them received IEAT.

Relative Factors of different EAT Prescriptions

Compared with patients receiving ANEAT, age was the only common relative factor of receiving IEAT (adjusted OR 1.022 [95%CI 1.012–1.032]; p < .001) and AUEAT (adjusted OR 1.010[95%CI 1.001–1.018]; p = .029) (Table 4). The odds of receiving IEAT and AUEAT increased with age. Patients with fever, respiratory disease, used mechanical ventilation, and sepsis or septic shock have higher odds of receiving AUEAT, but independent of receiving IEAT. Liver cirrhosis was a relative factor in patients received IEAT.

Table 4
Relative factors of EAT

	AUEAT(n = 398)			IEAT(n = 469)		
	crude OR (95%CI)	adjusted OR (95%CI)	P value	crude OR (95%CI)	adjusted OR (95%CI)	P value
Age	1.025(1.015–1.034)	1.023(1.013 ~ 1.032)	<.001	1.009(1.001–1.018)	1.009(1.001 ~ 1.018)	.033
Respiratory disease	2.176(1.538–3.079)	2.103(1.460 ~ 3.029)	<.001	/	/	
Liver cirrhosis	/	/	/	3.200(1.131–9.056)	0.252(0.086 ~ 0.737)	.012
Fever	1.930(1.320–2.822)	1.771(1.174 ~ 2.670)	.006	/	/	
Previous bloodstream infection	2.122(0.948–4.750)	1.396(0.587 ~ 3.319)	.450	/	/	
Vasopressor	2.513(1.615–3.909)	1.129(0.632 ~ 2.018)	.682	/	/	
Colloid	1.831(1.302–2.576)	0.944(0.616 ~ 1.447)	.793	0.621(0.445–0.868)	1.402(0.961 ~ 2.046)	.079
Mechanical ventilation	2.832(1.868–4.294)	2.214(1.326 ~ 3.696)	.002	0.494(0.325–0.752)	1.787(1.117 ~ 2.857)	.015
Sepsis or septic shock	3.070(2.020–4.664)	2.229(1.354 ~ 3.668)	.002	0.861(0.544–1.361)	0.916(0.557 ~ 1.506)	.729

OR: odds ratio. 95%CI: 95% confidence interval.

Outcomes Associated with Different EAT Prescriptions

Of the 1257 patients, 259 (20.6%) were admitted to ICU, with approximately 80% (202/259, 78.9%) of them received AUEAT or IEAT (Table 5). The median ICU LOS of patients who received AUEAT or IEAT was twice as long as those received ANEAT. The longest hospital LOS were in patients received IEAT, and it was similar in the other two groups. Hospital costs was higher in patients received AUEAT and IEAT. 261 (20.8%) patients had poor prognosis, including death or discharge against medical advice. Among them, 44.8% (117/261; p < .001) of patients received AUEAT, the percentage of patients received ANEAT and IEAT was similar (25.7%, 67/261 vs 29.5%, 77/261; p = .766).

Table 5
EAT and patient outcomes

	Total(n = 1257)	ANEAT(n = 390)	AUEAT(n = 398)	*P* value	IEAT(n = 469)	*P* value
ICU admission	259(20.6%)	57(14.6%)	94(23.6%)	.001	108(23.0%)	.002
ICU LOS, median (IQR), d	2.73(2.17–3.30)	1.52(0.97–2.07)	3.58(2.35–4.80)	.001	3.03(2.02–4.04)	.001
Hospital LOS, median (IQR), d	14(8–29)	13(7–24)	13(8–29)	.083	18(9–33)	<.001
Hospital costs, median (IQR), CNY	29,011(14,750 – 89,464)	23,578(12,563 – 66,335)	30,409(15,751 – 90,635)	<.001	35,695(15,942 – 107,810)	<.001
Poor prognosis	261(20.8%)	67(17.2%)	117(29.4%)	<.001	77(16.4%)	.766

LOS: length of stay.

Discussion

In our study, we found that more than two-thirds of infected inpatients were treated with AUEAT or IEAT. Improper and unnecessarily broad-spectrum antibiotics were common prevalent among hospitalized patients[21–23]. To investigate the prevalence of EAT prescriptions in different countries and regions is helpful to grasp the burden of unreasonable use of antibiotics in the world and improve antimicrobial stewardship. Patients received AUEAT and IEAT had higher rates of ICU admission, longer ICU LOS, and higher hospital costs. Received AUEAT was associated with an increased poor outcome, but we didn't find an association in received IEAT. These results differ from some previous studies on EAT [9,24–27]. Those researches were limited to severe infections such as bloodstream infection, ventilator-associated pneumonia, intra-abdominal infections or sepsis. But they could not represent of patients with infections of mild or moderate severity, which are more commonly encountered in clinical practice and therefore of great importance for overall antibiotic use and selection of resistant pathogens[28]. Received IEAT extended hospital LOS, while it was not found in receiving AUEAT. We speculate that this may be due to the fact that patients received AUEAT were worse off, as they were older and had a higher proportion of fever, treat with vasopressor, and use mechanical ventilation. Illness severity and age were independent predictors of mortality[29,30]. Actually, age and illness severity are correlated. The elderly adults are more likely to have bacterial infections or severe infection and the incidence of sepsis is disproportionately increased of them[30]. Clinicians make empirical antibiotic choices based on a combination of patient factors (older, illness severity, etc.), the suspected site of infection, the antimicrobial susceptibility of the expected pathogens, and local microbial resistance patterns[31,32], combined with current international guidelines and consensus. In patients received AUEAT are more likely to receive broad-spectrum antibiotic-probably unnecessarily-treatment as physicians want to ensure appropriateness most in severely ill patients[33], but it may not improve patient outcomes in fact.

We found that nearly half of the patients were infected with MDRO (included XDR and PDR), receipt of which was closely associated with treat with IEAT. The global dissemination of antimicrobial resistance further complicates empirical antibiotic decisions and is an independent risk factor for AUEAT and IEAT[34–36]. Antimicrobial resistance represents a major threat to human health with significant global and security implications and the latest report shows that disturbing high rates of resistance among antimicrobials frequently used to treat common bacterial infections[37]. The spread of resistant result in serious clinical and economic adverse outcomes, threatening the enormous gains made by the availability of antibiotic therapy[38]. In China, a range of policies have been introduced to curb antibiotic overuse and have achieved some success[39,40], but MDRO still prevalent nationwide. The China Antimicrobial Surveillance Network (CHINET) had been set up to monitor bacterial resistance of China since 2005. According to the annual report of CHINET (2021)[41], the situation of antibiotic resistance of bacteria represented by Gram-negative bacilli is severe, with the detection rate of the third generation cephalosporin-resistant *E.coli* strains remains high, and the detection rate of carbapenem-resistant *Klebsiella pneumoniae* keeps rising. Our research results are consistent with that. Early identification of pathogens and strengthening of antibiotic stewardship are the direction of efforts to reduce antimicrobial resistance and improve the accuracy of antibiotic prescription[42]. There is an urgent need for timely, rapid and accurate pathogen identification technology to assist clinicians in the formulation of treatment strategies. Hospitals should establish preferred empiric regimens for specific diseases and disease guidelines reduces the rate of inappropriateness of antibiotic treatment, taking into consideration local and national guidelines as well as antimicrobial susceptibilities[2,43]. And it is appropriate and prudent for hospitals to develop systems in which patients are expeditiously recognized and promptly treated with an antimicrobial regimen that is broad enough to cover all plausibly likely pathogens[8].

In our cohort, we found that more than two-thirds of patients with respiratory tract infection received AUEAT or IEAT. Respiratory tract infection is one of the most common diseases. It is responsible for great mortality, morbidity and high cost and EAT is the cornerstone of management of patients with pneumonia[44]. Patients with respiratory tract infections caused by *Klebsiella* and *Pseudomonas aeruginosa* had a large quantity of

cases and were more likely to receive AUEAT or IEAT. Those patients should be more careful in the empirical selection of antibiotics and further research is needed.

In terms of economic benefits, we found significant increases in hospital costs for both AUEAT and IEAT. Inappropriate and excessive use of antibiotics increases the burden of health care costs. Antimicrobial resistance has been shown to be associated with increased health care costs, and is likely the result of inadequate antibiotic therapy or may be related to the degree of severity of the underlying disease[45]. Appropriate antibiotic treatment can reduce the use of antibiotics, narrow antibiotic therapy, and decrease the costs for antibiotic.

There are some limitations in this study: 1) it was performed at a single center and could not representative of a larger population. 2) we could not distinguish between pathogenic bacteria and colonization bacteria based on existing data, which may have had a certain impact on the results. However, according to our exclusion criteria, we have excluded patients who are bacterial culture-positive but not treated with antibiotics, which means that clinicians have identified part of patients with colonized bacteria positive base on their expertise. 3) The Surviving Sepsis Campaign 2016[46] recommends that patients with sepsis and septic shock should be treated with IV antimicrobials within 1 h of recognition. It may be more suitable to evaluate the rationality of the antibiotic regimen on an hourly basis. However, it was not possible to analyze the time of antibiotic use on an hourly basis based on our database. Most of the subjects in our study were patients with mild infections. A study shown that in patients with mild to moderate disease a delay of therapy (e.g., by 4–8 h) has not been shown to be associated with worse clinical outcome[24].

Conclusions

In summary, inappropriate or unnecessarily broad-spectrum use of antibiotics is widely prevalent in hospital. AUEAT and IEAT were bound to increase antimicrobial resistance, rates of ICU admission, and health care costs. AUEAT was associated with increased odds of poor prognosis of patients. Near half of inpatients infected with MDRO (included XDR and PDR), and these patients were more likely to receive IEAT. The situation of antibiotic resistance of *Enterobacteriaceae* represented by *E. coli* and *Klebsiella* is most severe. Clinicians need to be more judicious in choosing antibiotic(s). Early identification of infectious pathogens and resistance can provide the basis for rational use of antibiotics and improve the current situation of antibiotic abuse and antimicrobial resistance.

Abbreviations

EAT
Empirical antibiotic therapy
AUEAT
Appropriate but unnecessarily broad-spectrum empirical antibiotic therapy
IEAT
Inappropriate empirical antibiotic therapy
ICU
Intensive care unit
SOFA
Sequential [Sepsis-related] Organ Failure Assessment
PCT
Procalcitonin
LOS
Length of stay
MDRO
Multidrug-resistant organism
XDR
Extensively drug resistant
PDR
Pandrug resistant
ANEAT
Appropriate and necessarily empirical antibiotic therapy
MRSA
Methicillin-resistant *Staphylococcus aureus*
VRE
Vancomycin-resistant *enterococci*
CTX-RO

Ceftriaxone-resistant Gram-negative organisms
ESBL
Extended-spectrum β-lactamase
OR
Odds ratios
CHINET
China Antimicrobial Surveillance Network.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Fifth Affiliated Hospital of Sun Yat-sen University (Zhuhai, China) (No. ZDWY [2022] Lunzi No. [K26-1]) with a waiver of informed consent.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article (and its additional information fles). The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yuting Luo, Zhaowang Guo, Ying Li, Jinyu Xia, and Xi Liu conceptualized and participated in the design of the study. Conductance of the study and data collection were performed by Yuting Luo, Hui Ouyang, Shanfeng Huang, Kenan Li, Yuxin Ji, Hongqiong Zhu, and Wentao Luo. Pathogen detection was performed by Zhaowang Guo. Data analysis was performed by Yuanli Chen, Yuting Luo, and Xi Liu. Yuting Luo, Zhaowang Guo, Ying Li, Jinyu Xia, and Xi Liu drafted the initial manuscript and all authors revised subsequent drafts. Yuting Luo, Zhaowang Guo, and Ying Li contributed equally to this manuscript. All authors read and approved the final manuscript for submission.

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Figures

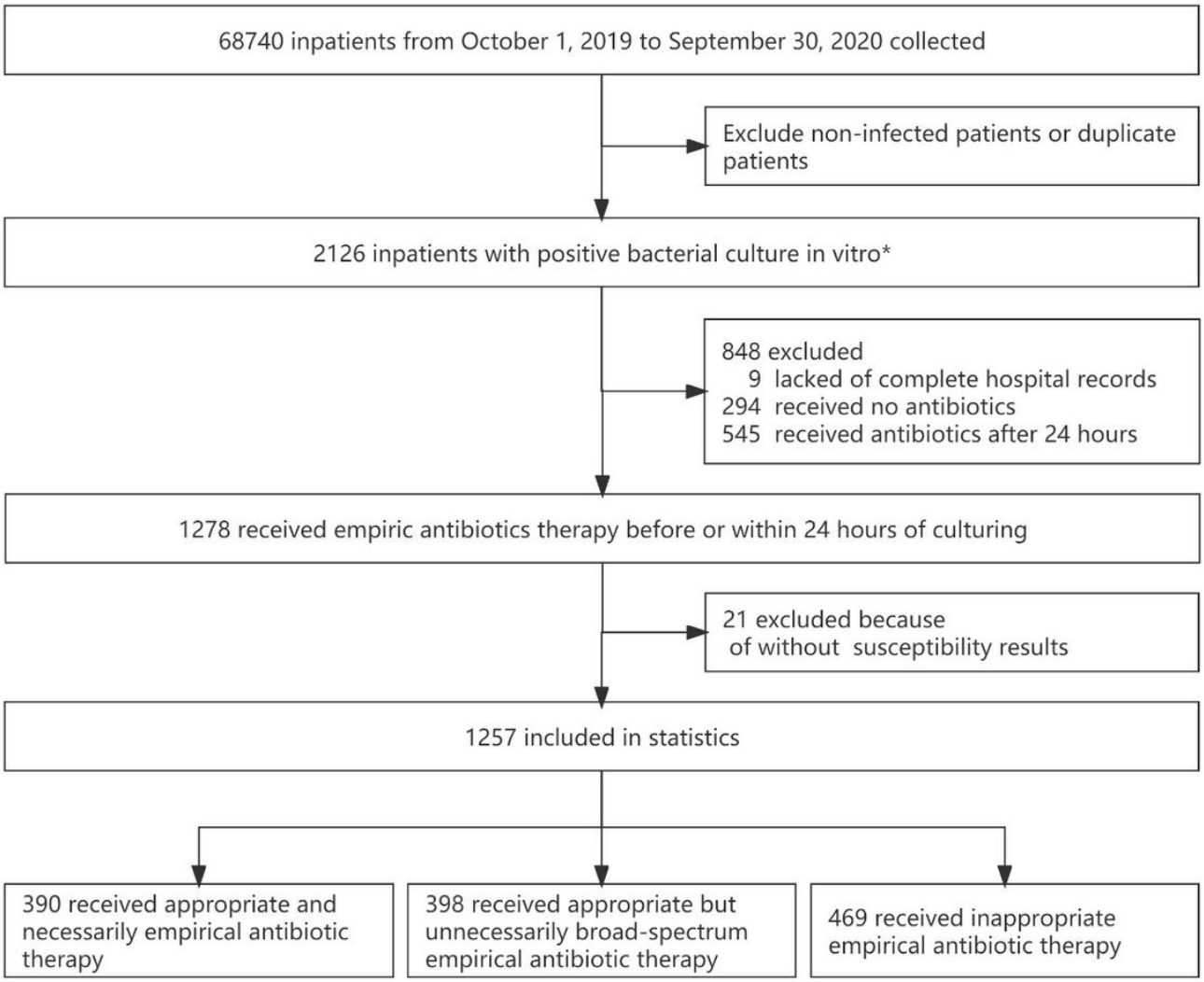

Figure 1

Case-selection flowchart

*Data of multiple hospitalizations were collected only once during the study period

Supplementary Files

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